

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 45/06, 31/435, 31/40, 31/135</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/36095</b> <b>(43) International Publication Date:</b> 22 July 1999 (22.07.99)
<b>(21) International Application Number:</b> PCT/SE98/02427 <b>(22) International Filing Date:</b> 22 December 1998 (22.12.98)  <b>(30) Priority Data:</b> 9800052-4 13 January 1998 (13.01.98) SE 9800330-4 5 February 1998 (05.02.98) SE  <b>(71) Applicant (for all designated States except MG US):</b> ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts WD4 8DH (GB).  <b>(71) Applicant (for MG only):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DIXON, John [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). INCE, Francis [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).  <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITIONS COMPRISING A COMPOUND HAVING DOPAMINE (D <sub>2</sub> ) RECEPTOR AGONIST ACTIVITY AND A COMPOUND (B) HAVING $\beta_2$ -ADRENORECEPTOR AGONIST ACTIVITY		
<b>(57) Abstract</b>  The present invention provides pharmaceutical compositions comprising a compound (A) having dopamine (D <sub>2</sub> ) receptor agonist activity and a compound (B) having $\beta_2$ -adrenoreceptor agonist activity. Preferably the composition comprises, as compound (A), cabergoline or ropinirole and as compound (B), formoterol, [R,R]-formoterol, salmeterol, [R]-salmeterol, [R]-salbutamol or terbutaline. The composition is used in the treatment of reversible obstructive airways diseases.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PHARMACEUTICAL COMPOSITIONS COMPRISING A COMPOUND HAVING DOPAMINE (D<sub>2</sub>) RECEPTOR AGONIST ACTIVITY AND A COMPOUND (B) HAVING  $\beta_2$ -ADRENORECEPTOR AGONIST ACTIVITY

The present invention relates to pharmaceutical compositions and their use in the treatment of reversible obstructive airways diseases.

In accordance with the present invention, there is provided a pharmaceutical composition comprising a compound (A) having dopamine (D<sub>2</sub>) receptor agonist activity and a compound (B) having  $\beta_2$ -adrenoreceptor agonist activity, wherein the compounds (A) and (B) are different.

In particular, the present invention provides a pharmaceutical composition comprising a compound (A) having dopamine (D<sub>2</sub>) receptor agonist selected from the group consisting of:

Apomorphine ((R)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol),

Bromocriptine ((5 $\alpha$ )-2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione),

Cabergoline ((8 $\beta$ )-N-[3-(dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)ergoline-8-carboxamide),

Lisuride (N'-[(8 $\alpha$ )-9,10-didehydro-6-methylergolin-8-yl]-N,N-diethylurea),

Pergolide ((8 $\beta$ )-8-[(methylthio)methyl]-6-propylergoline),

Levodopa (3-hydroxy-L-tyrosine),

Pramipexole ((S)-4,5,6,7-tetrahydro-N<sup>6</sup>-propyl-2,6-benzothiazolodiamine),

Quinpirole hydrochloride (trans-(-)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo[3,4-g]quinoline hydrochloride),

Ropinirole (4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one) and

Talipexole (5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo[4,5-d]azepin-2-amine)

and

a compound (B) having  $\beta_2$ -adrenoreceptor agonist activity selected from the

group consisting of:

Clenbuterol (4-amino-3,5-dichloro- $\alpha$ -[[[(1,1-dimethylethyl)amino]methyl]-benzenemethanol),

5 Fenoterol (5-[1-hydroxy-2-[[2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-1,3-benzenediol),

Formoterol (( $\pm$ )-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide),  
[R,R]-Formoterol,

10 Hexoprenaline (4,4'-[1,6-hexanediylbis[imino(1-hydroxy-2,1-ethanediyl)]]bis-1,2-benzenediol),

Isoetharine (4-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-1,2-benzenediol),

Isoprenaline (4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-1,2-benzenediol),

Metaproterenol (5-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-1,3-benzenediol),

Picumeterol (4-amino-3,5-dichloro- $\alpha$ -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]-methyl]benzenemethanol),

15 Pirbuterol ( $\alpha^6$ -[[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-2,6-pyridinedimethanol),

Procaterol ((R\*, S\*)-( $\pm$ )-8-hydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-2(1H)-quinolinone),

20 Reproterol (7-[3-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]propyl]-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione),

Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol),

Salbutamol (( $\pm$ )- $\alpha^1$ -[[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol),

[R]-Salbutamol,

25 Salmeterol (( $\pm$ )-4-hydroxy- $\alpha^1$ -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol),

[R]-Salmeterol,

Terbutaline (5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,3-benzenediol),

Tulobuterol (2-chloro- $\alpha$ -[[[(1,1-dimethylethyl)-amino]methyl]benzenemethanol) and

TA-2005 (8-hydroxy-5-[(1R)-1-hydroxy-2-[N-[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]carbostyryl hydrochloride).

The compounds (A) and (B) above are known to be used separately as pharmaceuticals  
5 but the use of a compound (A) in combination with a compound (B) in a pharmaceutical composition is not known.

Certain compounds (A) and (B) are capable of existing in stereoisomeric forms. Unless otherwise indicated, it should be understood that the invention encompasses the use  
10 of all geometric and optical isomers of compounds (A) or of compounds (B), and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

Preferably the composition comprises, as compound (A), cabergoline or ropinirole.  
15

The composition preferably comprises, as compound (B), formoterol, [R,R]-formoterol, salmeterol, [R-]-salmeterol, [R]-salbutamol or terbutaline.

The pharmaceutical composition of the invention may be prepared by mixing a  
20 compound (A) with a compound (B). Therefore, in another aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a compound (A) with a compound (B) as hereinbefore defined. The pharmaceutical composition of the invention may, and indeed will usually, contain various other ingredients known in the art, for example, a carrier, binder, lubricant, diluent,  
25 stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant. Thus the pharmaceutical composition of the invention will typically comprise a total amount of compound (A) and compound (B) (the active ingredients) in the range from 0.05 to 99 %w (per cent by weight), more preferably in the range from 0.10 to 70 %w, all percentages by weight being based on total composition.

The pharmaceutical compositions of the present invention have both  $\beta_2$ -adrenoreceptor agonist activity and dopamine ( $D_2$ ) receptor agonist activity.  $\beta_2$ -Adrenoreceptor agonist activity may be determined in a test carried out on the isolated trachea of the guinea pig according to the method of I.G. Dougall *et al.*, Br. J. Pharmacol., 1991, 104, 1057. Dopamine ( $D_2$ ) receptor agonist activity may be assessed by the binding  
5 affinities of compounds for the dopamine receptor binding sites in bovine pituitary membranes according to the method of D.R. Sibley *et al.*, J. Biol. Chem., 1982, 257(11), 6351-6361, or, in the functional rabbit isolated ear artery screen described by R. Brown *et al.*, Br. J. Pharmacol., 1981, 73, 189P.

10 The present pharmaceutical compositions are particularly suitable for use in the treatment of reversible obstructive airways diseases such as asthma (including bronchial asthma, allergic asthma and intrinsic asthma, e.g. late asthma and airway hyper-responsiveness), chronic bronchitis and other chronic obstructive pulmonary diseases.

15 Thus, the present invention further provides a pharmaceutical composition as hereinbefore defined for use in therapy.

In a further aspect, there is provided the use of a pharmaceutical composition as  
20 hereinbefore defined in the manufacture of a medicament for the treatment of reversible obstructive airways disease, in particular for the treatment of asthma or chronic bronchitis.

The present invention still further provides a method of treating, or reducing the risk of, a reversible obstructive airways disease in a patient suffering from, or at risk of, said  
25 disease, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compounds (A) and (B) employed, the mode of administration, the treatment  
30 desired and the disorder indicated. However, in general, satisfactory results will be

obtained when the pharmaceutical composition is administered such that the total daily dosage of compound (A) and compound (B) together is in the range from 5 to 1500  $\mu\text{g}$ , e.g. from 10 to 1450  $\mu\text{g}$  or from 20 to 1400  $\mu\text{g}$ .

5       The pharmaceutical composition of the invention may be administered topically (to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

10

For example metered dose inhaler devices may be used to administer the active ingredients, dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents.

15

Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Especially preferred propellants are P134a and P227, each of which may be used alone or in combination with other propellants and/or surfactants and/or other excipients.

20

Nebulised aqueous suspensions or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulations.

25

Dry powder inhalers may be used to administer the active ingredients, alone or in combination with a pharmaceutically-acceptable carrier, in the latter case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

30

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

Tablets and gelatin capsules, which may be coated if desired, containing the active ingredients may, for example, also include one or more diluents, carriers, binders, lubricants or stabilising agents.

5

Injectable solutions of the active ingredients may also contain, for example, one or more preservatives, stabilising agents, viscosity-regulating agents, emulsifying agents or buffering agents.



## CLAIMS

1. A pharmaceutical composition comprising a compound (A) having dopamine ( $D_2$ ) receptor agonist activity and a compound (B) having  $\beta_2$ -adrenoreceptor agonist activity,  
5 wherein the compounds (A) and (B) are different.
2. A composition according to Claim 1 comprising a compound (A) having dopamine ( $D_2$ ) receptor agonist activity selected from the group consisting of apomorphine, bromocriptine, cabergoline, lisuride, pergolide, levodopa, pramipexole, quinpirole  
10 hydrochloride, ropinirole and talipexole, and a compound (B) having  $\beta_2$ -adrenoreceptor agonist activity selected from the group consisting of clenbuterol, fenoterol, formoterol, [R,R]-formoterol, hexoprenaline, isoetharine, isoprenaline, metaproterenol, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, salbutamol, [R]-salbutamol, salmeterol, [R]-salmeterol, terbutaline, tulobuterol and TA-2005.  
15
3. A composition according to Claim 2, wherein, as compound (A), cabergoline or ropinirole is used.
4. A composition according to Claim 2, wherein, as compound (B), formoterol,  
20 [R,R]-formoterol, salmeterol, [R]-salmeterol, [R]-salbutamol or terbutaline is used.
5. A pharmaceutical composition as claimed in any one of Claims 1 to 4 for use in therapy.
- 25 6. Use of a pharmaceutical composition as claimed in any one of Claims 1 to 4 in the manufacture of a medicament for the treatment of reversible obstructive airways disease.

7. A method of treating, or reducing the risk of, a reversible obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition as defined in any one of Claims 1 to 4.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02427

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/435, A61K 31/40, A61K 31/135  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4590206 A (RAYMOND B. FORRESTER ET AL), 20 May 1986 (20.05.86), column 4, lines 42-57 --	1-7
Y	US 5551489 A (EVA A. C. TROFAST ET AL), 3 Sept 1996 (03.09.96), claims --	1-7
Y	US 5288498 A (THEODORE H. STANLEY ET AL), 22 February 1994 (22.02.94), claims 1, 39, 67, 73, 77 --	1-7



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

21 April 1999

Date of mailing of the international search report

29 -04- 1999

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Anneli Jönsson  
Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02427

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>Thorax, Volume 34, 1979, K M Christensen et al, "A double-blind trial of bromocriptine in steroid dependent asthma", page 284 - page 285, page 284, column 1, lines 1-9; column 1, line 41 - column 2, line 4; column 2, line 9 - line 10</p> <p style="text-align: center;">-- -----</p>	1-7

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02427

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Claim 7 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claims. The search has been based on the alleged effects of the composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.

PCT/SE 98/02427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4590206 A	20/05/86	AT 17441 T	15/02/86
		AU 540826 B	06/12/84
		AU 8635582 A	10/02/83
		BE 893912 A	24/01/83
		CA 1187415 A	21/05/85
		CH 657273 A,B	29/08/86
		DK 159716 B,C	26/11/90
		DK 325982 A	25/01/83
		EP 0072046 A,B	16/02/83
		SE 0072046 T3	
		FI 822548 A	25/01/83
		FR 2510405 A	04/02/83
		GB 2105189 A,B	23/03/83
		GR 76229 A	04/08/84
		HK 10088 A	12/02/88
		IE 53640 B	04/01/89
		JP 4068285 B	02/11/92
		JP 58059914 A	09/04/83
		LU 84291 A	07/02/83
		PT 75310 B	29/11/85
		US 5260306 A	09/11/93
		ZA 8205222 A	25/05/83
US 5551489 A	03/09/96	AU 7826194 A	01/05/95
		CZ 9600942 A	12/06/96
		EP 0721331 A	17/07/96
		FI 961430 A	29/03/96
		HU 74519 A	28/01/97
		HU 9600821 D	00/00/00
		IL 111080 D	00/00/00
		NO 961290 A	29/03/96
		PL 175564 B	29/01/99
		PL 313765 A	22/07/96
		SE 9303214 D	00/00/00
		SE 9304271 D	00/00/00
		WO 9509615 A	13/04/95
		ZA 9407533 A	03/04/95
		AU 679789 B	10/07/97
		BR 9407686 A	04/02/97
		IL 113023 D	00/00/00
		JP 9504224 T	28/04/97
		NZ 274277 A	26/01/98
		SE 9400896 D	00/00/00
		SK 39196 A	04/06/97
		CN 1132476 A	02/10/96
		SG 48049 A	17/04/98

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.

PCT/SE 98/02427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5288498 A	22/02/94	AT 138562 T	15/06/96
		AU 642664 B	28/10/93
		AU 6337190 A	08/04/91
		CA 2066403 A,C	06/03/91
		DE 69027216 D,T	17/10/96
		DK 490944 T	21/10/96
		EP 0490944 A,B	24/06/92
		SE 0490944 T3	
		ES 2089027 T	01/10/96
		JP 2749198 B	13/05/98
		JP 5500058 T	14/01/93
		US 5855908 A	05/01/99
		WO 9103236 A	21/03/91
		AT 116131 T	15/01/95
		CA 1271421 A	10/07/90
		CA 1338978 A	11/03/97
		CA 1339190 A	29/07/97
		DE 3650189 D,T	04/05/95
		EP 0200490 A,B	05/11/86
		SE 0200490 T3	
		EP 0404205 A,B	27/12/90
		SE 0404205 T3	
		EP 0487520 A,B	03/06/92
		SE 0487520 T3	
		EP 0490891 A,B	24/06/92
		SE 0490891 T3	
		US 4671953 A	09/06/87
		US 4863737 A	05/09/89
		US 4885173 A	05/12/89
		US 5122127 A	16/06/92
		US 5132114 A	21/07/92
		US 5288497 A	22/02/94
		US 5484602 A	16/01/96
		WO 9103099 A	07/03/91
		WO 9103234 A	21/03/91
		US 5783207 A	21/07/98
		US 5785989 A	28/07/98